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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/820,133

04/08/2004

James L. Hartley

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8634

26111

7590

05/18/2005

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WASHINGTON, DC 20005

EXAMINER

MARVICH, MARIA

ART UNIT

PAPER NUMBER

1636

DATE MAILED: 05/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/820,133

Applicant(s)

HARTLEY ET AL.

Examiner

Maria B. Marvich, PhD

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 17 February 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 2-29 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 2-29 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 08 April 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

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### **DETAILED ACTION**

This office action is in response to an amendment filed 2/17/05. No claims have been amended. Claims 2-29 are pending in the application.

#### ***Response to Amendment***

Any rejection of record in the previous action not addressed in this office action is withdrawn. There are no new grounds of rejection herein and therefore, this action is final.

#### ***Claim Rejections - 35 USC § 112, second paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 2-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This rejection is maintained for reasons of record in the office action mailed 11/17/04.**

Claims 2-29 are vague and indefinite in that the metes and bounds of “recombination site or portions thereof” are unclear. Applicants recite use of specific primers that are comprised of “recombination sites or portions thereof” as primers for synthesis of double stranded nucleic acids. By reciting, “recombination sites or portions thereof”, the structural requirements of the primers are unclear. Is it required that the sites are involved in site-specific recombination or can sites for random integration or homologous recombination be used in the instant invention?

***Response to Argument***

Applicants traverse the claim rejections under 35 U.S.C. 112, second paragraph on pages 13-14 of the amendment filed 2/17/05. Applicants argue that the term “recombination site” refers to “site-specific recombination sites”. Applicants argue that as regards the term “portions thereof”, the specification provides a definition. Based upon the definition, a person of skill in the art would readily understand the term.

Applicants’ arguments filed 2/17/05 have been fully considered but they are not persuasive. As the claims do not explicitly recite that the sites are “site-specific recombination sites”, it is unclear what the structural requirements of the sites are. As to “portions thereof”, it is unclear how a portion of a recombination site that can be as small as 2 base pairs can function in the recited method to generate a DNA molecule with a recombination site on the end. The claims appear to require a site-specific recombination site such that molecules can be generated that can be used in recombinational cloning. However, by recitation of “recombination site and portions thereof”, the metes and bounds of the recited sites are unclear.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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Claims 2-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hartley et al (WO 96/40724; see entire document) in view of Shuman (US 5,766,891; see entire document).

**This rejection is maintained for reasons of record in the office action mailed 11/17/04.**

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Applicants claim a method for synthesizing a double stranded nucleic acid molecule using primers corresponding to first and second recombination sites wherein the recombination sites either comprise mutations that remove one or more stop codon, avoid hairpin formation or are sequence with 80-90% homology to SEQ ID NOs: 1-16 or 39-43. These sequences comprise derivatives of *attB*, *attP*, *attL*, *attR*, *lox* recombination sites. The first and second recombination sites do not recombine with one another. Furthermore, applicants claim recombination sites that are located at or near one and/or both terminus of the resultant double-stranded molecule. The first and second recombination sites do not recombine with one another.

Hartley et al teaches methods of generating DNA and vectors having engineered recombination sites for use in recombination cloning (see e.g. page 1, line 10-15). Insert and Donor sequences comprise double stranded DNA with recombination sites at either end to enhance recombinational cloning of the insert into the Donor (see e.g. page 28, line 20-29). The

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recombination sites are identical to those recited in SEQ ID NO:s 1-16 and 39-43 and thus they inherently contain mutations that eliminate stop codons and the ability to form hairpin formations as described in the instant specification and described by Hartley et al on page 39, 42. Furthermore, use of any two sequences together in a PCR reaction would not result in recombination of one primer with another (see e.g. page 27, line 22 through page 28, line 20). Specifically, Hartley et al disclose SEQ ID NOs: 1-16 and 39-43 (see e.g. sequence listing and page 29, line 4 through page 30, line 9). Hartley et al contemplate primer sites for PCR by juxtaposition of two DNA sequences that were not previously juxtaposed (see e.g. page 20, line 15-17).

Hartley et al do not explicitly teach methods of generating the insert or Donor DNA sequences such as by PCR amplification.

Shuman discloses methods of synthesizing double-stranded DNA molecules by PCR amplification. The resultant molecule comprises the primer sequences at each 5' and 3' end (see e.g. col 6, line 46-56). Shuman uses topoisomerase recognition sites for primer sequences (see e.g. col 16, line 57-65).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to generate the double-stranded molecules to be used in recombination by Hartley et al with the method of PCR taught by Shuman because Hartley et al teach that it is within the ordinary skill of the art to generate double-stranded molecules with recombination sites at either end for recombinational cloning and because Shuman teaches that it is within the ordinary skill of the art to generate double-stranded molecules for cloning using PCR. One would have been motivated to do so in order to receive the expected benefit of generating sub-cloning systems that

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are highly specific, rapid and less labor intensive (see e.g. Hartley, page 6, line 18-26). Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

### ***Response to Argument***

Applicants traverse the claim rejections under 35 U.S.C. 103(a) on pages 15-17 of the amendment filed 2/17/05. Applicants argue that the examiner has not met the burden of establishing a *prima facie* case of obviousness based upon the prior art. According to applicants, the rejection lacks motivation or suggestion to combine the references.

Applicants' arguments filed 2/17/05 have been fully considered but they are not persuasive. To establish motivation, three sources are permitted- the nature of the problem to be solved, the teachings of the prior art, and the knowledge of a person of ordinary skill in the art. In the instant case, Hartley et al described methods of using double stranded DNAs that have recombination sequences at either end. The sequences are to be used in recombinational cloning. In order to generate insert and donor sequences to be used in the recombinational cloning methods of Hartley et al, the insert and donor sequences must be generated such that recombination sites are at each end. To this end, Hartley et al teach that PCR can be used to primer sites for PCR by juxtaposition of two DNA sequences that were not previously juxtaposed (see e.g. page 20, line 15-17). At another section, Hartley et al teaches that primer sites can be inserted or annealed to existing vectors (see e.g. example 46). At the time of the instant invention, it was well known that recombinant vectors comprising heterologous

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sequences could be generated by PCR amplification using sequences comprising the heterologous sequences. This method involves the juxtaposition of two DNA sequences that were not previously juxtaposed and is detailed in Shuman et al. Therefore, the nature of the problem to be solved in both cases is the generation of sequences for cloning which is taught by Shuman et al to be solved by PCR amplification with primers that are then added to the ends of the sequence. Furthermore, this technique is well known in the art to function to generate DNA molecules with juxtaposed sequences.

### ***Conclusion***

No Claims allowed.

1. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.



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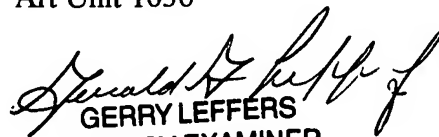
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

May 11, 2005

Maria B Marvich, PhD  
Examiner  
Art Unit 1636

  
GERRY LEFFERS  
PRIMARY EXAMINER